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EXAMINER	
DAVIS, MINH TAM B	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/555,342	Applicant(s) KATO ET AL.	
	Examiner MINH-TAM DAVIS	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 September 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-17,19-21 and 25-32* is/are pending in the application.

4a) Of the above claim(s) *11-13,19-21 and 29-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-17,25-28 and 32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 4 (4 sheets).
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's election without traverse of group II, claims 14-17, 25-28, 32 in Paper No. 7 is acknowledged.

Accordingly, claims 14-17, 25-28, 32 are examined in the instant application.

PRIORITY DATE

Acknowledgment is made of applicant's claim for foreign priority based on applications PCT/JP 98/05348, and JP 342060/1997 filed in Japan on 10/22/98 and 10/27/97, respectively. It is noted, however, that applicant has not filed a certified copy of the above applications as required by 35 U.S.C. 119(b). Accordingly, the priority date of the instant application SN=09/555342 is determined to be 05/26/2000.

SEQUENCE RULE COMPLIANCE

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. 1.821-25 for the the following reasons:

The figures 1, 3, 4 legends do not contain sequence identification numbers for the recited sequences.

Claim Objections

OK

Claim 32 is objected to because of the following informalities: Claim 32 recites non-elected inventions (inventions of claims 11-13, 19-21). Appropriate correction is required.

Claim Rejections - 35 USC § 112, SECOND PARAGRAPH

Claims 14-17, 32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

OK

1. Claims 14-16 and 32 are indefinite because claims 14-16 and 32 depend on non-elected claims 11, 12, 13, and (11-13, 19-21, and 29), respectively.

2. Claim 17 is indefinite because it is drawn to stringent hybridization conditions. Stringent conditions are not defined by the claim (which reads on the full range of stringent conditions, that is from very permissive to very high stringency), Yet the specification only describes one stringent condition. The specification does not provide a standard for ascertaining the requisite degree of stringent conditions and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention and would not be able to determine the metes and bounds of the claims.

OK? Check support for amended claims? 16? Plus 20-21 OK?

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement

thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

1. Claims 14-17 and 32 are rejected under 35 USC 101, because the claimed invention is directed to non-statutory subject matter.

Claims 14-17 and 32 are drawn to 1) DNA encoding a protein specifically expressed in differentiated chondrocytes, comprising an ezrin-like domain, a Db1 domain, and a pleckstrin domain, 2) DNA encoding a protein of SEQ ID NO:2, 3) DNA encoding a protein that has 85% homology to amino acids 1-374, or 544-737, or 764-854 of SEQ ID NO:2, 4) a gene comprising DNA comprising nucleotides 49-3183 of SEQ ID NO:1, or DNA which hybridizes under stringent conditions with DNA comprising nucleotides 49-3183 of SEQ ID NO:1, and which encodes a protein specifically expressed in differentiated chondrocytes, and 5) a kit comprising any one of said DNA.

The DNA or gene as claimed has the same characteristics and utility as a DNA or gene found naturally and therefore do not constitute patentable subject matter. In the absence of the hand of man, the naturally occurring polypeptide is considered non-statutory subject matter. Diamond v. Chakrabarty, 206 USPQ 193 (1980). Amendment of the claims to recite " an isolated DNA or gene" is suggested to overcome this rejection..

2. Claims 14-17, 25-28 and 32 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific asserted utility or a well established utility.

Claims 14-17, 25-28 and 32 are drawn to 1) DNA encoding a protein specifically expressed in differentiated chondrocytes, comprising an ezrin-like domain, a Db1 domain, and a pleckstrin domain, 2) DNA encoding a protein of SEQ ID NO:2, 3) DNA encoding a protein that has 85% homology to amino acids 1-374, 544-737, and 764-854 of SEQ ID NO:2, 4) a gene comprising DNA comprising nucleotides 49-3183 of SEQ ID NO:1, or DNA which hybridizes under stringent conditions with DNA comprising nucleotides 49-3183 of SEQ ID NO:1, and which encodes a protein specifically expressed in differentiated chondrocytes, 5) an isolated nucleic acid molecule of SEQ ID NO:1 or fragments thereof that encode at least 90 amino acids of SEQ ID NO:2, 6) an isolated nucleic acid molecule that is complementary to SEQ ID NO:1, or fragments thereof that encode at least 90 amino acids of SEQ ID NO:2, and 7) a kit comprising any one of said DNA or nucleic acid molecules.

The specification discloses isolation of a CDEP clone that is expressed in chondrocytes but not in dedifferentiated chondrocytes, by substractive hybridization (p.26, first paragraph). The specification further discloses that CDEP mRNA is detected as two bands of 3.5 kb and 5 kb in various human fetal tissues (brain, spleen, heart, liver and intestine), wherein the nucleotide sequence corresponding to the transcript of 5 kb is not known (p.26, last paragraph bridging p. 27, and p.27, second paragraph). In adult tissues, CDEP mRNA is expressed mainly in kidney, testis, and lung (p.27, second paragraph). In addition, the specification discloses that CDEP has 1) a domain which is 27% similar to ezrin, and 43 % similar to band 4.1 known in the art (p.10, second paragraph), 2) a DH domain which is 22% similar to Db1, Ost, Ect2 of the

oncogene Rho GEF family, and 25% similar to FGD1, a causative gene for faciogenital dysplasia, and 3) a PH domain at the C-terminus (p.11, first paragraph). Moreover, since the claimed gene is expressed in cartilage, and other tissues, the claimed gene could be useful for osteoarthritis, and rheumatoid arthritis (p.33, last paragraph, bridging p. 34). In addition, in view of the structural feature of the claimed gene, having an ezrin-like domain, a DH and PH domain, the claimed gene serves as a regulatory factor for cytoskeleton, and may play an important role in the reconstruction of a cytoskeleton, which occurs as a result of stimulation by cell growth factors or cell transformation (p.34). Further, for chondrocytes, changes in cell shape are closely related to differentiation, it may be possible to induce or maintain the differentiation of chondrocytes. The specification further disclose the use of the claimed invention for detecting differentiated chondrocytes, screening regulators of cell differentiation induction, which is an anti-tumor agent (p. 4-5).

However, neither the specification nor any art of record teaches what CDEP is, what it does do, they do not teach a utility for any of the fragments claimed. They do not teach a relationship to any specific diseases or establish any involvement in the etiology of any specific diseases. The asserted utilities for CDEP, such as production of and screening of antibodies apply to many unrelated polypeptide structures sequences. Therefore the asserted utilities are not considered "specific" utilities, i.e. they are not specific to CDEP. Additional disclosed utilities for CDEP include therapy of diseases such as osteoarthritis, and rheumatoid arthritis, and screening regulators of cell differentiation induction, which is an anti-tumor agent. The asserted utility of the CDEP

is based on the assertion that the CDEP, (SEQ ID NO:1) has regions that are homologous to ezrin, Db1, and pleckstrin. In particular CDEP has 1) a domain which is 27% similar to ezrin, and 43 % similar to band 4.1 known in the art (p.10, second paragraph), 2) a DH domain which is 22% similar to Db1, Ost, Ect2 of the oncogene Rho GEF family, and 25% similar to FGD1, a causative gene for faciogenital dysplasia. It is noted that the specification does not teach that there are consensus sequences required for the erzin, Db1 and pleckstrin activity of the encoded protein. It is clear that, although CDEP has 1) a domain which is 27% similar to ezrin, and 43 % similar to band 4.1 known in the art (p.10, second paragraph), 2) a DH domain which is 22% similar to Db1, Ost, Ect2 of the oncogene Rho GEF family, and 25% similar to FGD1, there is a 73%, 57%, 78% and 75% dissimilarity between SEQ ID NO:1 and the sequences of erzin, band 4.1, Db1, and FGD1, respectively, and the effects of these dissimilarities upon protein structure and function cannot be predicted. Bowie et al (Science, 1990, 257:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable

expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar et al (Molecular and Cellular Biology, 1988, 8:1247-1252) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. Clearly, with 73%, 57%, 78% and 75% dissimilarity between SEQ ID NO:1 and the sequences of erzin, band 4.1, Db1, and FGD1, respectively, the function of the SEQ ID NO:1 polypeptide could not be predicted, based on sequence similarity, nor would it be expected to be the same as that of erzin, band 4.1, Db1, and FGD1. In addition, Bork (Genome Research, 2000,10:398-400) clearly teaches the pitfalls associated with comparative sequence analysis for predicting protein function because of the known error margins for high-throughput computational methods. Bork specifically teaches that computational sequence analysis is far from perfect, despite the fact that sequencing itself is highly automated and accurate (p. 398, col 1). One of the reasons

for the inaccuracy is that the quality of data in public sequence databases is still insufficient. This is particularly true for data on protein function. Protein function is context dependent, and both molecular and cellular aspects have to be considered (p. 398, col 2). Conclusions from the comparison analysis are often stretched with regard to protein products (p. 398, col 3). Furthermore, recent studies show that alternative splicing might affect more than 30% of human genes and the number of known post-translational modifications of gene products is increasing constantly so that complexity at protein level is enormous. Each of these modifications may change the function of respective gene products drastically (p. 399, col 1). Further, although gene annotation via sequence database searches is already a routine job, even here the error rate is considerable (p. 399, col 2). Most features predicted with an accuracy of greater than 70% are of structural nature and at best only indirectly imply a certain functionality (see legend for table 1, page 399). As more sequences are added and as errors accumulate and propagate it becomes more difficult to infer correct function from the many possibilities revealed by database search (p. 399para bridging cols 2 and 3). The reference finally cautions that although the current methods seem to capture important features and explain general trends, 30% of those feature are missing or predicted wrongly. This has to be kept in mind when processing the results further (p. 400, para bridging cols 1 and 2).

Further, Scott et al (Nature Genetics, 1999, 21:440-443) teach that the gene causing Pendred syndrome encodes a putative transmembrane protein designated pendrin. Based on sequence similarity data, the authors postulated that the putative

protein was deemed to be a member of sulfate transport proteins that included a 29% identity to rat sulfate-anion transporter, 32% similarity to human diastrophic dysplasia sulfate transporter, and 45% similarity to the human sulfate transporter 'downregulated in adenoma'. However, upon analyzing the expression and kinetics of the protein, the data revealed no evidence of sulfate transport wherein results revealed that pendrin functioned as a transporter of chloride and iodide. Scott et al. suggest that these results underscore the importance of confirming the function of newly identified gene products even when the database searches reveal significant homology to proteins of known function (page 411, 1st column, 4th paragraph).

Clearly, given not only the teachings of Bowie et al, Lazar et al, Burgess et al and Scott et al, but also the limitations and pitfalls of using computational sequence analysis and the unknown effects of alternative splicing, post translational modification and cellular context on protein function as taught by Bork, with a 73%, 57%, 78% and 75% dissimilarity between SEQ ID NO:1 and the sequences of erzin, band 4.1, Db1, and FGD1, respectively, the function of the SEQ ID NO:1 polypeptide could not be predicted, based on sequence similarity, nor would it be expected to be the same as that of erzin, band 4.1, Db1, and FGD1. Further, even if the polypeptide of SEQ ID NO:1 is an erzin, band 4.1, Db1, and FGD1-like protein, neither the specification nor any art of record teaches what the polypeptide is, what it does, does not teach a relationship to any specific disease or establish any involvement of the polypeptide in the etiology of any specific disease or teach which fragments might be active or would function as claimed

In addition, the claimed nucleic acid is not specific for differentiated chondrocytes, because it is detected in various fetal and adult tissues, such as adult kidney, testis, and lung which do not necessarily have differentiated chondrocytes, and because the disclosed probe is not specific for SEQ ID NO:1, as indicated by the detection of two bands, wherein the sequence of the detected 5kb band is not known.

Moreover, even if the claimed nucleic acid is specific for differentiated chondrocytes, the utility of the claimed nucleic is not specific, because it is shared by other nucleic acids that are specific for differentiated chondrocytes.

. The specification essentially gives an invitation to experiment wherein the artisan is invited to elaborate a functional use for the disclosed nucleic acids. Because the claimed invention is not supported by a specific asserted utility for the reasons set forth, credibility of any utility cannot be assessed.

Claim Rejections - 35 USC § 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION

Claims 16, 17, 27-28, 32 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 16, 17, 27-28, 32 are drawn to 1) DNA encoding a protein comprising an amino acid sequence of SEQ ID NO:2, in which one to several amino acids have been deleted, substituted or added, wherein said protein has 85% homology to amino acids

1-374, 544-737, and 764-854 of SEQ ID NO:2, 2) DNA which hybridizes under stringent conditions with DNA comprising nucleotides 49-3183 of SEQ ID NO:1, and which encodes a protein specifically expressed in differentiated chondrocytes, 3) an isolated nucleic acid molecule that is complementary to SEQ ID NO:1, or fragments thereof that encode at least 90 amino acids of SEQ ID NO:2, and 7) a kit comprising any one of said DNA or nucleic acid molecules.

It is noted that DNA encoding a protein in which one to several amino acids have been deleted, substituted or added, wherein said protein has 85% homology to amino acids 1-374, 544-737, and 764-854 of SEQ ID NO:2 encompasses DNA encoding variants of SEQ ID NO:2. It is further noted that a DNA sequence could hybridize under stringent conditions to nucleotides 49-3183 of SEQ ID NO:1 via a common fragment. It is also noted that a complement could be partial or complete, wherein a partial complement could share with SEQ ID NO:1 or fragments thereof only a few common nucleotides.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

The teaching of *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412) are clearly relevant to the instant rejection. The court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

The specification discloses a protein that has 85% homology to amino acids 1-374, 544-737, and 764-854 of SEQ ID NO:2 (p.13). No further description of variants by substitution is provided in the specification. The claims 16, 17, 27-28 however read on a nucleotide sequence encoding variants of SEQ ID NO:2, wherein said variants have any type of substitution besides conservative substitution, at any amino acid, throughout the length of amino acids 1-374, 544-737, and 764-854 of SEQ ID NO:2, as well as insertions and deletions. The specification and the claims do not place any limit on which amino acid to be subjected to conservative or non-conservative substitution, the type of substitution besides conservative substitution, nor the type of amino acids replacing the original amino acids. In addition, the specification and all other pending claims do not place any limit on the number of amino acids that could be substituted,

deleted or added, provided the upper limit of the variation is 15%. Thus the scope of the claims includes nucleotide sequences encoding numerous structural variants. Although the types of changes are routinely done in the art, the specification and the claims do not provide any guidance as to which, or how many original amino acid(s) to be substituted, or to which type of substitution besides conservative substitution, or which amino acids could be deleted or inserted so that the claimed polypeptide could function as contemplated. Structural features, that could distinguish the claimed nucleotide sequences encoding said variants from the nucleotide sequences known in the art, are missing from the disclosure. No common structural attributes that identify the claimed nucleotide sequences encoding said variants are disclosed. In addition, no common functional attributes that identify the claimed nucleotide sequences encoding said variants are disclosed, because the function of a nucleotide sequence could be abolished, even with substitution of only one amino acid of the peptide encoded by said nucleotide sequence (Burgess et al. Journal of Cell Biology, 1990, 11: 2129-2138). In addition, although conservative substitution would not destroy the biological function of a protein, the specification fails to disclose which amino acid(s) would be subjected to conservative substitution. The general knowledge and level of skill in the art do not supplement the omitted description, because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the claimed nucleotide sequences encoding said variants, SEQ ID NO:1 alone is insufficient to describe nucleotide sequences encoding said variants. One of skill in the art would reasonably conclude that the disclosure fails to provide a

representative number nucleotide sequences encoding said variants. Thus, applicant was not in possession of the claimed nucleotide sequences encoding said variants.

Thus, there is insufficient support of claims 16, 17, 27-28 as provided by the Interim Written Description Guidelines published in the June 5, 1998 Federal Register at Volume 63, Number 114, pages 32639-32645. Therefore, only isolated polynucleotide of SEQ ID NO:1, but not the full breadth of the claims meets the written description provision of 35 USC 112, first paragraph.

Claim Rejections - 35 USC § 112, FIRST PARAGRAPH, ENABLEMENT

Claims 14-17, 25-28, and 32 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Specifically, since the claimed invention is not supported by either a specific and credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 112, FIRST PARAGRAPH, SCOPE

1. If Applicant could overcome the above 101 and 112, first paragraph rejection, claim 16 is still rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling SEQ ID NO:1, does not reasonably provide enablement for a nucleotide sequence encoding a variant of SEQ ID NO:2. The specification does not

enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims.

Claim 16 is drawn to DNA encoding a protein, comprising an amino acid sequence of SEQ ID NO:2, in which one to several amino acids have been deleted, substituted or added, wherein 1) the amino acid sequence of a portion of said protein "corresponding' to an amino acid sequence ranging from the first to 374th amino acids of SEQ ID NO:2 has 85% or more homology with the amino acid sequence ranging from the first to 374th amino acids of SEQ ID NO:2, 2)) the amino acid sequence of a portion of said protein "corresponding' to an amino acid sequence ranging from the 544th to 737th amino acids of SEQ ID NO:2 has 85% or more homology with the amino acid sequence ranging from the 544th to 737th amino acids of SEQ ID NO:2, and 3)) the amino acid sequence of a portion of said protein "corresponding' to an amino acid sequence ranging from the 764th to 854th amino acids of SEQ ID NO:2 has 85% or more homology with the amino acid sequence ranging from the 764th to 854th amino acids of SEQ ID NO:2.

The scope of the claims includes nucleotide sequences encoding numerous structural variants. Applicants have not shown how to make and use the claimed DNA sequences encoding the polypeptide variants which are capable of functioning as that which is being disclosed.

Protein chemistry is probably one of the most unpredictable areas of biotechnology. Such unpredictability would equally apply to DNA sequences which encode proteins. For example, replacement of a single lysine residue at position 118 of

acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein (Burgess et al. Journal of Cell Biology, 1990, 11: 2129-2138). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (Lazar et al. Molecular and Cell Biology, 1988, 8: 1247-1252). Similarly, it has been shown that aglycosylation of antibodies reduces the resistance of the antibodies to proteolytic degradation, while CH2 deletions increase the binding affinity of the antibodies (see Tao. et al. The Journal of Immunology, 1989, 143(8): 2595-2601, and Gillies et al. Human Antibodies and Hybridomas, 1990, 1(1): 47-54). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein.

In view of the above unpredictability, one of skill in the art would be forced into undue experimentation in order to perform the claimed invention as broadly as claimed.

In addition, although conservative subsititution would not destroy the biological function of a protein, the specification fails to disclose which amino acid(s) would be subjected to conservative substitution. In the absence of a source of method of making such variants, one of skill in the art would be forced into undue experimentation to practice the claimed invention as broadly as claimed.

2. If Applicant could overcome the above 101 and 112, first paragraph rejection, claims 17, 27-28, 32 are still rejected under 35 U.S.C. 112, first paragraph, because the

specification, while being enabling SEQ ID NO:1, does not reasonably provide enablement for a nucleotide sequence which hybridizes under stringent conditions with DNA comprising nucleotides 49-3183 of SEQ ID NO:1, and complements of SEQ ID NO:1 or complements of a fragment thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims.

Claims 17, 27-28, 32 are drawn to 1) DNA which hybridizes under stringent conditions with DNA comprising nucleotides 49-3183 of SEQ ID NO:1, and which encodes a protein specifically expressed in differentiated chondrocytes, 2) an isolated nucleic acid molecule that is complementary to SEQ ID NO:1, or fragments thereof that encode at least 90 amino acids of SEQ ID NO:2, and 3) a kit comprising any one of said DNA or nucleic acid molecules.

Claims 17, 27-28, 32 encompass polynucleotides comprising non-disclosed nucleic acid sequences attached to nucleotides 49-3183 of SEQ ID NO:1 or to SEQ ID NO:1 or fragments thereof. That is polynucleotides that hybridize to nucleotides 49-3183 of SEQ ID NO:1 under stringent conditions and are complementary to SEQ ID NO:1 or fragments thereof. When given the broadest reasonable interpretation, the claims are clearly intended to encompass a variety of species including full-length cDNAs, genes and protein coding regions. Clearly, it would be expected that a substantial number of the hybridizing or complementary polynucleotides encompassed by the claims **would not** share either structural or functional properties with nucleotides 49-3183 of SEQ ID NO:1 or fragments thereof. The specification fails to provide an enabling disclosure for

how one would use such polynucleotides. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art on how to use the broadly claimed species. For the above reasons, undue experimentation would be required to practice the claimed invention.

3. If Applicant could overcome the above 101 and 112, first paragraph rejection, claims 14-17, 26, 28, 32 are still rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling SEQ ID NO:1, does not reasonably provide enablement for a nucleotide sequence which "encodes" a protein of SEQ ID NO:2 or variants thereof, or a fragment thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims.

Claims 14-17, 26, 28 and 32 are drawn to 1) DNA encoding a protein specifically expressed in differentiated chondrocytes, comprising an ezrin-like domain, a Db1 domain, and a pleckstrin domain, 2) DNA encoding a protein of SEQ ID NO:2, 3) DNA encoding a protein that has 85% homology to amino acids 1-374, 544-737, and 764-854 of SEQ ID NO:2, 4) DNA which hybridizes under stringent conditions with DNA comprising nucleotides 49-3183 of SEQ ID NO:1, and which encodes a protein specifically expressed in differentiated chondrocytes, 5) an isolated nucleic acid molecule that comprises a fragments of SEQ ID NO:1, that encode at least 90 amino acids of SEQ ID NO:2, 6) an isolated nucleic acid molecule that is complementary to a

fragments of SEQ ID NO:1, that encode at least 90 amino acids of SEQ ID NO:2, and 7) a kit comprising any one of said DNA or nucleic acid molecules.

The specification discloses detection of CDEP protein in a lung fibroblast cell line (Example 4, on pages 32-33).

One cannot extrapolate the teaching of the specification to the claims, because it is unpredictable that CDEP protein is expressed in tissues in nature. Detection of CDEP protein in a lung fibroblast cell line does not mean that CDEP protein would be detected in tissue samples, because characteristics of cells in culture are different from characteristics of cells in tissues *in vivo*. Although drawn mostly to cancer cell lines in culture, the following teaching would apply as well to any cell types in culture, wherein cell culture artifacts are well known in the art. Drexler et al (Leukemia and Lymphoma, 1993, 9:1-25) specifically teach, in the study of Hodgkin and Reed-Sternberg cancer cells in culture, that the acquisition or loss of certain properties during adaptation to culture systems cannot be excluded and that only a few cell lines containing cells that resemble the *in-vivo* cancer cells have been established and even for the *bona fide* cancer cell lines it is difficult to prove that the immortalized cells originated from a specific cancer cell (see attached abstract). Further, Embleton et al (Immunol Ser, 1984, 23:181-207) specifically teaches that in procedures for the diagnosis of osteogenic sarcoma, caution must be used when interpreting results obtained with monoclonal antibodies that had been raised to cultured cell lines and specifically teach that cultured tumor cells may not be antigenically typical of the tumor cell population from which they were derived and it is well established that new artifactural antigens

can occur as a result of culture (see attached abstract). Hsu (in Tissue Culture Methods and Applications, Kruse and Patterson, Eds, 1973, Academic Press, NY, see abstract, p.764) specifically teaches that it is well known that cell cultures *in vitro* frequently change their chromosomal constitutions (see abstract). The evidence presented clearly demonstrates that in cell culture systems, in general, and in cancer derived cell lines in particular, that artifactural chromosome constitutions and antigen expression are expected and must be taken into account when interpreting data received from cell line assays. Further, Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, petri dish cancer is a poor representation of malignancy, with characteristics profoundly different from the human disease Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary -type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is

stable and differentiated to one that is not, yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interations. Thus, based on the cell culture data presented in the specification, it could not be predicted that CDEP protein is expressed in tissues *in vivo*.

Further, although CDEP mRNA is expressed in various tissues, those of skill in the art recognize that expression of mRNA, specific for a tissue type, does not dictate nor predict the translation of such mRNA into a polypeptide. For example, Alberts et al. (Molecular Biology of the Cell, 3rd edition, 1994, page 465) teach that translation of ferritin mRNA into ferritin polypeptide is blocked during periods of iron starvation. Likewise, if excess iron is available, the transferrin receptor mRNA is degraded and no transferrin receptor polypeptide is translated. Many other proteins are regulated at the translational level rather than the transcriptional level. For instance, Shantz and Pegg (Int J of Biochem and Cell Biol., 1999, Vol. 31, pp. 107-122) teach that ornithine decarboxylase is highly regulated in the cell at the level of translation and that translation of ornithine decarboxylase mRNA is dependent on the secondary structure of the mRNA and the availability of eIF-4E, which mediates translation initiation. McClean and Hill (Eur J of Cancer, 1993, vol. 29A, pp. 2243-2248) teach that p-glycoprotein can be overexpressed in CHO cells following exposure to radiation, without

any concomitant overexpression of the p-glycoprotein mRNA. In addition, Fu et al (EMBO Journal, 1996, Vol. 15, pp. 4392-4401) teach that levels of p53 protein expression do not correlate with levels of p53 mRNA levels in blast cells taken from patients with acute myelogenous leukemia, said patients being without mutations in the p53 gene. Thus, predictability of protein translation or the extent of translation is not solely contingent on mRNA expression due to the multitude of homeostatic factors affecting transcription and translation. For the above reasons, one of skill in the art would not be able to predict if SEQ ID NO:1 is translated into a polypeptide expression product. In view of the above, one of skill in he art would be forced into undue experimentation to practice the claimed invention.

Moreover, the claimed encoded protein comprising an ezrin-like domain, "a Db1 domain, and a pleckstrin domain" does not seem to exist in nature. The specification discloses that CDEP has 1) a domain which is 27% similar to ezrin, and 43 % similar to band 4.1 known in the art (p.10, second paragraph), 2) a DH domain which is 22% similar to Db1, Ost, Ect2 of the oncogene Rho GEF family, and 25% similar to FGD1, a causative gene for faciogenital dysplasia. In other words, the disclosed encoded protein has domains that are similar to erzin, Db1 and pleckstrin. However the disclosed encoded protein does not have domains that are identical to "a Db1 domain, and a pleckstrin domain". Since the structure of a sequence is unpredictable, unless isolated and sequenced, and since the claimed encoded protein having an ezrin-like domain, "a Db1 domain, and a pleckstrin domain" has not been isolated, nor detected, it is

questionable that the claimed encoded protein having an ezrin-like domain, "a Db1 domain, and a pleckstrin domain" exists in nature.

For the above reasons, undue experimentation would be required to practice the claimed invention.

4. If Applicant could overcome the above 101 and 112, first paragraph rejection, claim 32 is still rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling a kit for identifying a differentiated chondrocyte from a dedifferentiated chondrocyte, does not reasonably provide enablement for a kit for identifying a differentiated cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims.

Claim 32 is drawn to a kit for identifying a differentiated cell. Claim 32 encompasses a kit for identifying any differentiated cell.

The specification discloses isolation of a CDEP clone that is expressed in differentiated chondrocytes but not in dedifferentiated chondrocytes, by substractive hybridization (p.26, first paragraph). The specification further discloses that CDEP mRNA is detected as two bands of 3.5 kb and 5 kb in various human fetal tissues (brain, spleen, heart, liver and intestine), wherein the nucleotide sequence corresponding to the transcript of 5 kb is not known (p.26, last paragraph bridging p. 27, and p.27, second paragraph). In adult tissues, CDEP mRNA is expressed mainly in kidney, testis, and lung (p.27, second paragraph). No disclosure is found in the

specification concerning how to distinguish differentiated cells from non-differentiated cells, and whether CDEP mRNA is expressed in any non-differentiated cells.

One cannot extrapolate the teaching in the specification to the claims because , without a reference point for comparison, and without a teaching of how to distinguish differentiated cells from non-differentiated cells, it would not be possible to identify any differentiated cells using the claimed invention. Although the claimed gene is expressed in differentiated chondrocytes, and fibroblasts, it is unpredictable that the expression of the claimed gene is different between non-differentiated cells, such as stem cells, and differentiated cells. It is well known in the art that expression of a gene is hightly regulated (Shantz, LM et al, 1999, Internatl J Biochem & Cell Biol, 31: 107-122), and thus its expression in a certain type of tissue is unpredictable unless tested.

For the above reasons, undue experimentation would be required to practice the claimed invention.

withdrawn

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 17, 25, 27 are rejected under 35 U.S.C. 102(b) as being anticipated by Koyano Y et al, 1997, BBRC, 241(2): 369-375, and Genbank Sequence Database (Accession AB008430), National Center for Biotechnology Information, National Library of Medicine, Bethesda, Maryland, publicly available on 1997.

Claims 17, 25, 27 are drawn to 1) a gene comprising DNA comprising nucleotides 49-3183 of SEQ ID NO:1, 2) an isolated nucleic acid molecule of SEQ ID NO:1 and 3) an isolated nucleic acid molecule that is complementary to SEQ ID NO:1.

Koyano Y et al teach a sequence which is 100% similar to the entire length of the claimed SEQ ID NO:1 from nucleotide 1 to 3422, under MPSRCH sequence similarity search report (MPSRCH search report, us-09-555-342a-1.rge, pages 1-3).

Given the polynucleotide sequence taught by Koyano Y et al, one of ordinary skill in the art would immediately envision the claimed polynucleotides.

withdrawn

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.

Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 32 is rejected under 35 U.S.C. 103(a) as being unpatentable over Koyano Y et al, *supra*.

Claim 32 is drawn to a kit for identifying a differentiated cell comprising 1) a gene comprising DNA comprising nucleotides 49-3183 of SEQ ID NO:1, 2) an isolated nucleic

acid molecule of SEQ ID NO:1 and 3) an isolated nucleic acid molecule that is complementary to SEQ ID NO:1.

The recitation of the language "for identifying a differentiated cell" is merely suggestive of an intended use and is not given weight for purposes of comparing the claims with the prior art. The claims read on the active ingredients *per se*, which are 1) a gene comprising DNA comprising nucleotides 49-3183 of SEQ ID NO:1, 2) an isolated nucleic acid molecule of SEQ ID NO:1 and 3) an isolated nucleic acid molecule that is complementary to SEQ ID NO:1.

The teaching of Koyano Y et al has been set forth above. Koyano Y et al however does not teach a kit comprising a nucleotide sequence.

It would have been *prima facia* obvious to a person of ordinary skill in the art at the time the invention was made to make the sequence taught by Koyano Y et al in a kit, because it is common in the art to make and use a kit comprising a compound for commercial purposes. One of ordinary skill in the art would have been motivated to make the sequence taught by Koyano Y et al in a kit with a reasonable expectation of success.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 703-305-2008. The examiner can normally be reached on 9:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, ANTHONY CAPUTA can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4426 for regular communications and 703-308-4426 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0916.

MINH TAM DAVIS
December 12, 2001